General

Guideline Title

American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti–TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease.

Bibliographic Source(s)

Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT, AGA Institute Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-a biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013 Dec;145(6):1459-63. [2 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of evidence (high, moderate, low, very low) and strength of recommendation (strong, weak) are provided at the end of the "Major Recommendations" field.

Recommendations for Induction of Remission

1. The guideline developers suggest against using thiopurine monotherapy to induce remission in patients with moderately severe Crohn's disease (CD) (Weak Recommendation, Moderate-Quality Evidence)
2. The guideline developers suggest against using methotrexate to induce remission in patients with moderately severe CD (Weak Recommendation, Low-Quality Evidence)
3. The guideline developers recommend using anti–tumor necrosis factor (TNF)-α drugs to induce remission in patients with moderately severe CD (Strong Recommendation, Moderate-Quality Evidence)
4. The guideline developers recommend using anti–TNF-α monotherapy over thiopurine monotherapy to induce remission in patients who have moderately severe CD (Strong Recommendation, Moderate-Quality Evidence)
5. The guideline developers recommend using anti–TNF-α drugs in combination with thiopurines over thiopurine monotherapy to induce remission in patients who have moderately severe CD (Strong Recommendation, High-Quality Evidence)
6. The guideline developers suggest using anti–TNF-α drugs in combination with thiopurines over anti–TNF-α drug monotherapy to induce remission in patients who have moderately severe CD (Weak Recommendation, Moderate-Quality Evidence)

Recommendations for Maintenance of Remission

7. The guideline developers recommend using thiopurines over no immunomodulator therapy to maintain a corticosteroid-induced remission in patients with CD (Strong Recommendation, Moderate-Quality Evidence)
8. The guideline developers suggest using methotrexate over no immunomodulator therapy to maintain corticosteroid-induced remission in patients with CD (Weak Recommendation, Low-Quality Evidence)
9. The guideline developers recommend using anti–TNF-α drugs over no anti–TNF-a drugs to maintain corticosteroid- or anti–TNF-α-induced remission in patients with CD (Strong Recommendation, High-Quality Evidence)
10. The guideline developers make no recommendation for or against the combination of an anti–TNF-α drug and a thiopurine versus an anti–TNF-α drug alone to maintain remission induced by a combination of these drugs in patients with CD (No Recommendation, Low-Quality Evidence)

Definitions:

Quality of Evidence

Quality of Evidence	Estimate of Certainty of Effect
High	Further research is very unlikely to change the estimate of effect
Moderate	Further research is likely to have an important impact and may change the estimate of effect
Low	Further research is very likely to have an important impact and is likely to change the estimate of effect
Very low	Any estimate of effect is uncertain

Note: The quality of evidence was ranked in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

Strength of Recommendation

Strong	Based on the available evidence, the benefits outweigh risks and there is less variability in patient's values and preferences.
Weak	Based on the available evidence, the benefits, risks, and the burden of intervention are more closely balanced, or appreciable uncertainty exists in regards to patient's values and preferences.

Clinical Algorithm(s)

An interactive algorithm titled "Use of Biologic Drugs for Inflammatory Crohn's Disease: Clinical Decision Support Tool" is available from the American Gastroenterological Association Institute Web site .

Scope

Disease/Condition(s)

Inflammatory Crohn's disease

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Gastroenterology

Internal Medicine

Intended Users

Physicians

Guideline Objective(s)

To inform clinical decision making as well as to establish quality of care indicators by making transparent and actionable recommendations

Target Population

Patients with Crohn's disease

Interventions and Practices Considered

1. Thiopurine monotherapy
2. Methotrexate
3. Anti-tumor necrosis factor (TNF)-α monotherapy
4. Anti-TNF-α/thiopurine combination therapy

Major Outcomes Considered

- Corticosteroid-free clinical remission
- Disease relapse, corticosteroid use, or surgery
- Serious infections and lymphoma

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Three separate literature searches were conducted: one for evidence summaries (such as meta-analyses); one for randomized controlled trials (RCTs) for the efficacy, infection, and lymphoma outcomes; and one for observational evidence to supplement the data on infection and lymphoma. An information specialist developed each search with input from the project team. All search results were imported using bibliographic management software for de-duplication and title and abstract screening.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE. Parallel searches included the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register, and Health Technology Assessment (HTA) Database. The search strategy comprised controlled vocabulary, including the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concepts included and combined were "Crohn disease" and "immunomodulator therapy" and "anti-tumor necrosis factor." Methodological filters were applied to limit retrieval to RCTs, meta-analyses, systematic reviews, and health technology assessments. The results were limited to English, human, and 1995 onward. The second search consisted of the main search concepts "Crohn disease" and "immunomodulator therapy" and "anti-tumor necrosis factor" plus "lymphoma." The results were limited to English language and 2010 onward, because prior systematic reviews using appropriate search strategies had adequately covered earlier time frames. A search for observational

evidence on harm was performed from this search (see Supplementary Methods for the detailed search strategies). Updated information on serious infection and lymphoma (The Crohn's Therapy, Resource, Evaluation, and Assessment Tool [TREAT] registry) became available during the writing process and was thus included in this review.

For more information on excluded and included studies and search strategies, refer to the technical review (see the "Availability of Companion Documents" field).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

Quality of Evidence	Estimate of Certainty of Effect
High	Further research is very unlikely to change the estimate of effect
Moderate	Further research is likely to have an important impact and may change the estimate of effect
Low	Further research is very likely to have an important impact and is likely to change the estimate of effect
Very low	Any estimate of effect is uncertain

Note: The quality of evidence was ranked in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Based on the literature searches, the guideline developers identified existing systematic reviews and used AMSTAR, a validated instrument, to evaluate the quality of systematic reviews. Systematic reviews that were of high quality, were up-to-date, and used the outcomes of interest (e.g., corticosteroid-free remission based on Crohn's Disease Activity Index [CDAI]) were selected for inclusion in the evidence profiles. When systematic reviews were not up-to-date or were incomplete, the guideline developers performed their own meta-analysis (random effects model for 3 or more studies and fixed effects model for 2 studies) using the Cochrane Collaboration's RevMan 5.1 software.

Harm data from randomized controlled trials (RCTs) were sometimes of inadequate quality or had very few events. When this occurred, the guideline developers identified observational studies and assessed them for risk of bias using the Newcastle-Ottawa tool. The guideline developers selected the observational studies with the highest methodological quality and greatest number of events for the outcomes of serious infections and lymphoma.

For more information on study evaluation, refer to the technical review (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

Description of Methods Used to Formulate the Recommendations

This clinical practice guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and was drafted by an American Gastroenterological Association (AGA) Institute Guideline Panel, reviewed by the Clinical Practice and Quality Management Committee, and approved by the AGA Institute Governing Board. The guideline is published in conjunction with a technical review on the same subject, and interested readers are encouraged to refer to that publication for in-depth consideration of topics covered by this guideline (see the "Availability of Companion Documents" field).

To develop this document, the members of the guideline panel met with the authors of the technical review in Chicago on March 16, 2013. Also attending the meeting were the current and incoming chairs of the AGA Clinical Practice and Quality Management Committee, senior members of the AGA staff, and a consumer representative. The authors of the technical review presented to the group the results of the systematic review of the evidence for each clinical question to be addressed in the guideline, organized in the PICO format (population, intervention, comparator, and outcome). For each PICO, the group came to an agreement regarding the overall quality of the evidence, the balance between desirable and undesirable effects, patient values and preferences regarding the desirable and undesirable effects, and whether or not the intervention in question represents a prudent use of resources.

Using the PICO format, the guideline developers outlined a total of 16 PICO questions. Based on these parameters, the members of the guideline panel then reached consensus regarding a recommendation for or against each intervention and rated the strength of the recommendation as either strong or weak. Strong recommendations were made when (1) the overall quality of the evidence was moderate or high regarding the efficacy and safety of the intervention, (2) there was little or no uncertainty regarding the balance of desirable and undesirable effects of the intervention, (3) there was little or no uncertainty regarding a patient's values and preferences regarding the intervention and its effects, and (4) there was little or no uncertainty as to whether or not the intervention was too costly given the expected benefits.

The implication of a strong recommendation is that most patients should receive the recommended course of action and that adherence to this recommendation could be used as a quality of care indicator. The implication of a weak recommendation is that the course of action is suggested but that additional factors, such as the patient’s values and preferences, will need to be considered. The majority of fully informed patients would still want to follow this course of action, but many would not. The final decision regarding the course of action would be the product of shared decision making between the health care provider and patient.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

Strong	Based on the available evidence, the benefits outweigh risks and there is less variability in patient's values and preferences.
Weak	Based on the available evidence, the benefits, risks, and the burden of intervention are more closely balanced, or appreciable uncertainty exists in regards to patient's values and preferences.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document presents the official recommendations of the American Gastroenterological Association (AGA) Institute on the use of thiopurines,

methotrexate, and anti–tumor necrosis factor (TNF)-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease (CD). It was drafted by an AGA Guideline Panel, reviewed by the Clinical Practice and Quality Management Committee, and approved by the AGA Institute Governing Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is provided for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of thiopurines, methotrexate, and anti-tumor necrosis factor (TNF)-α biologic drugs for induction and maintenance of remission in patients with inflammatory Crohn's disease (CD)

Potential Harms

- There are very rare reports that associate use of methotrexate with an increased risk of lymphoma.
- Although high-quality data are lacking, it does appear that long-term use of thiopurines is associated with a 1.5- to 5-fold increased risk of lymphoma and with a possibly slightly higher risk of serious infection, although the absolute rates of these adverse events are low.
- Opportunistic infections, such as tuberculosis or fungal infections, can occur as a direct consequence of use of the anti–tumor necrosis factor (TNF)-α drugs.
- Anti–TNF-α drug/thiopurine combination therapy is associated with an increase in the rate of lymphoma.

Contraindications

Contraindications

Patients who want to conceive cannot use methotrexate.

Qualifying Statements

Qualifying Statements

- Medical Position Statements are derived from the data available at the time of their creation and may need to be modified as new information is generated. Unless otherwise stated, these statements are intended for adult patients.
- These documents are not to be construed as standards of care. All decisions regarding the care of a patient should be made by the physician in consideration of all aspects of the patient's specific medical circumstances. A comprehensive background paper, the Technical Review, provides the user of the Medical Position Statement with the evidence used to formulate a particular recommendation and the strength and character of that evidence.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT, AGA Institute Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-a biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013 Dec;145(6):1459-63. [2 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Dec

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Institute Clinical Practice and Quality Management Committee

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Financial Disclosures/Conflicts of Interest

The authors disclose the following: Dr Dudley-Brown has served as a consultant for Shire and as an advisory board member for Salix, Centocor, and UCB. The remaining authors disclose no conflicts.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Gastroenterology Journal Web site .

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

Availability of Companion Documents

The following is available:

- American Gastroenterological Association technical review on the use of thiopurines, methotrexate, and anti–TNF-a biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013 Jan;145(12):1464-1478. Electronic copies: Available from the Gastroenterology Journal Web site .

Patient Resources

None available

NGC Status

This summary was completed by ECRI Institute on March 25, 2014. The information was verified by the guideline developer on April 25, 2014.

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